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Case 2206

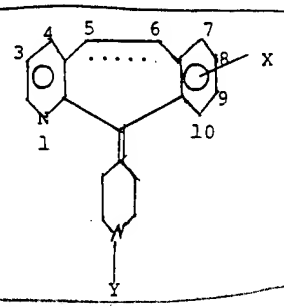
Antihistaminic ~~NOVEL~~ 11-(4-PIPERIDYLIDENE)-5H-BENZO-[5,6]-CYCLOHEPTA-[1,2,-b]-PYRIDINES

The present invention relates to novel 11-(4-piperidylidene)-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridines.

United States Patent 3,326,924 discloses 6,11-dihydro-11-(N-methyl-4-piperidylidene)-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridine and 11-(N-methyl-4-piperidylidene-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridine, useful as antihistamines.

The compounds of the present invention are likewise useful as antihistamines, but are preferred to the compounds of the aforementioned patent because the present compounds have little or no sedative effects, thus being preferred for use with patients that must operate machinery or automobiles or perform other mental or physical tasks requiring a high level of concentration.

The compounds of the present invention are compounds of the formula



(I)

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P1061 06/26/80 160795 19-0365 2 101 65.00CH
P1062 06/26/80 160795 19-0365 2 102 58.00CH
5677 07/18/80 160795 19-0365 1 102 44.00CH

wherein the dotted line represents an optional double bond and wherein the numbering system used herein is illustrated. In this formula, X is hydrogen or halo and Y is substituted carboxylate or substituted sulfonyl.

In a preferred embodiment of the present invention, Y is -COOR and R is C_1 to C_6 alkyl or substituted alkyl, phenyl, ~~sub~~substituted phenyl, C_7 to C_{12} aralkyl or ~~phenyl-~~substituted aralkyl or -2,-3 or -4 piperidyl or N-substituted piperidyl. When R is substituted alkyl, R is substituted with amino or with substituted amino. The substituents on said substituted amino are C_1 to C_6 alkyl. The substituents on the aforementioned substituted phenyl and on the phenyl moiety of th ~~phenyl-~~substituted aralkyl are preferably C_1 to C_6 alkyl or halo.

In a second preferred embodiment of the present invention, Y is SO_2R and R is C_1 to C_6 alkyl, phenyl, substituted phenyl, C_7 to C_{12} aralkyl or ~~phenyl-~~substituted aralkyl, wherein the substituents on said substituted phenyl and on the phenyl moiety of the ~~phenyl-~~substituted aralkyl are C_1 to C_6 alkyl or halo.

The aforementioned alkyl groups may be linear, branched or cyclic or may contain both cyclic and linear or cyclic and branched moieties. Halo may be fluoro, chloro, bromo or iodo.

The present invention also relates to a pharmaceutical composition comprising an effective amount of a compound of the formula I as defined above, together with a pharmaceutically acceptable carrier and to a method of effecting an anti-allergic response in an animal comprising administering to the animal an effective amount of a compound of the formula I as defined above.

Generally, compounds of the present invention are prepared by replacing a methyl or another replacable substituent, for example carbophenoxy on the nitrogen of the piperidylidene ring of an appropriate compound of the formula I with the desired substituent.

For example, compounds of the formula I wherein Y is $\frac{1}{m}$COOR are prepared by reacting a compound of the formula I wherein Y is methyl (Compound IA) or an appropriate derivative of Compound IA with an appropriate chloroformate, for example, an alkylchloroformate or phenyl chloroformate in order to replace the N-methyl group on the piperidylidene group of Compound IA.

Compounds of the formula I wherein Y is $\frac{1}{m}$COOR may also be prepared by reacting a compound of the formula I wherein Y is $\frac{1}{m}$COOR and R is phenyl with the sodium salt of an appropriate alcohol.

Compounds of the formula I wherein Y is $\frac{1}{m}$COOR and R is tert-butyl may be prepared by reacting a compound of the formula I wherein Y is hydrogen with a di-tertiarybutyl carbonate in an inert solvent, for example, tetrahydrofuran.

Compounds of the formula I wherein Y is $\frac{1}{m}SO_2R$ are prepared by reacting a compound of the formula I wherein Y is hydrogen with a compound of the formula $Cl\frac{1}{m}SO_2R$, wherein R has the same value as R in the desired product, in the presence of an excess of anhydrous potassium carbonate in an inert solvent, for example dry toluene.

DEP The following non-limiting Examples further illustrate the preparation of the compounds of the present invention:

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CL CL/C Example 1

A. 11-(N-Carboethoxy-4-piperidylidene)-6,11-dihydro-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridine

(8,9) P

To a solution of 10.9 g (0.1 mole) of ethylchloroformate in 300 ml. of anhydrous benzene is added dropwise, with stirring at room temperature, a solution of 14.5 g (0.05M) of 11-(N-methyl-4-piperidylidene)-6,11-dihydro-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridine (Compound IA) in 200 ml of benzene. The solution is stirred and is heated under reflux overnight ($16\frac{1}{N}20$ hrs.). The mixture is cooled and is poured into ice water and the organic layer is separated, washed with water, dried, and then concentrated to dryness. The residue is triturated with petroleum ether and a white solid having a melting point of $106\frac{1}{N}107^{\circ}_{20}C$ is recrystallized from isopropyl ether after decolorization with decolorizing carbon.

CL

B. 11-(N-Carboethoxy-4-piperidylidene)-8-chloro-6,11-dihydro-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridine

(8,9) P

Using the procedure of Example IA, react 16.2 g of the 8-chloro derivative of Compound IA and 10.9 g (0.1 mole) of ethylchloroformate to prepare the title compound, having a melting point of $128\frac{1}{N}130^{\circ}_{20}C$. The 7,9 and 10-chloro analogues are similarly prepared.

CL

C. 11-(N-Carbomethoxy-4-piperidylidene)-6,11-dihydro-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridine

(8,9) P

Using the procedure of Example IA, react 14.5 g of Compound IA and 9.4 g of methylchloroformate to prepare the title compound, having a melting point of $116\frac{1}{N}118^{\circ}_{20}C$.

Cl 4/c

Example 2

11-(N-Carbophenoxy-4-piperidylidene)-6,11-dihydro-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridine (Compound IB)

To a solution of 29.1 g (0.1 mole) of Compound IA in 150 ml. of anhydrous carbon tetrachloride is added 17 g of phenylchloroformate in an equal volume of anhydrous carbon-tetrachloride. Heat under reflux for 15 minutes with stirring and pour into water. Separate and wash the organic layer with water and remove solvent. Extract the residue with ether, filter off the insoluble material and remove the ether. The residue is recrystallized from isopropyl ether to yield the title compound having a melting point of $127\frac{I}{N}130^{\circ}C_{20}$.

Similarly prepare the 7,8,9, or 10-chloro derivatives of the title compound using this procedure:

Cl 4/c

Example 3

11-(N-Carboisopropoxy-4-piperidylidene)-6,11-dihydro-5H-benzo-[5,6]-cyclohepta-[1,2-b] pyridine

Dissolve 0.5 g sodium metal in 50 ml isopropanol and add 7.9 g of Compound IB from Example 2. Heat with stirring for 5 hours on the steam bath at $90\frac{I}{N}95^{\circ}_{20}$ and allow to cool overnight.

Add ice water to precipitate the product and extract 3 times with ether and once with chloroform. Wash with water, distill off solvents, triturate with hexane and recrystallize from isopropylether. The melting point is $147\frac{I}{N}148^{\circ}C_{20}$.

Using this procedure and replacing the isopropanol with n-butanol, cyclopentanol, allylalcohol, cyclopropylmethanol, benzylalcohol, p-chlorobenzylalcohol, phenethylalcohol, dimethylaminoethylalcohol or N-methyl-4-hydroxy piperidine prepare the corresponding carbamoyl derivatives. Similarly, using the chloro derivatives of Compound IB and the sodium salts of the aforementioned alcohols, prepare the chloro derivatives of the aforementioned carbamoyl derivatives.

Cl % Example 4

Cl 11-(N-Carbo-t-butoxy-4-piperidylidene)-6,11-dihydro-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridine. (8,9)

P Dissolve 13.8 g of 11-(4-piperidylidene)-6,11 dihydro-5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridine (Compound IC) prepared according to Villani et. al., J. Med. Chem. 15, 750 (1972) in 250 ml of dry tetrahydrofuran. With stirring, add in one portion 12 g of di-tbutyl carbonate and stir at room temperature overnight. The mixture is poured into water, is extracted with ether, is washed with water and the solvent removed. Recrystallize the residue from ispropyl ether. The melting point is 144 1/N 145 °C. 20

(8,9)

6/17/80

Cl % Example 5

B Cl 11-(N-Methanesulfonyl-4-piperidylidene)-6,11-dihydro--5H-benzo-[5,6]-cyclohepta-[1,2-b]-pyridine. (8,9)

P To 10 g of Compound IC in 200 ml of dry toluene add 13 g of anhydrous potassium carbonate. After several minutes of stirring at room temperature, add dropwise a solution of

6 g of methanesulfonyl chloride in 20 ml of toluene. Continue stirring for 16 to 20 hours and then filter. Recrystallize the solid material from ethanol. The melting point is 223-224°C.

Using this procedure and adjusting the weight of the requisite sulfonyl chloride so that 0.04 moles of said alkanesulfonyl chloride are used, the ethanesulfonyl, n-propylsulfonyl, n-butylsulfonyl, cyclopropylsulfonyl, heptylsulfonyl, dodecylsulfonyl, phenylsulfonyl, p-methylphenyl-sulfonyl, p-fluorophenylsulfonyl, p-chlorophenylsulfonyl, benzylsulfonyl, p-chlorobenzylsulfonyl, p-tertbutylphenylsulfonyl and cyclopentylsulfonyl compounds of formula I wherein Y is SO_2R are obtained.

Similarly, prepare the tricyclic ring substituted chloro derivatives.

Substituting the appropriate starting material having a double bond between the 5 and 6 positions of the ring system, and using the procedures set forth in Examples 1 to 5 above for the corresponding 6,11-dihydro compounds, the corresponding 6,11-dehydro compounds are prepared. Also, by substituting the appropriate bromo or other halo analogue, as desired, of the chloro compounds of the Formula I used as starting materials, the desired halo compounds of the formula I are prepared.

The compounds of the present invention are useful as non-sedating antihistamines. These compounds act as anti-allergic agents in the treatment of such conditions as perennial and seasonal allergic rhinitis and chronic urticaria.

The compounds of the present invention are administered in pharmaceutical formulations comprising the compound in admixture with a pharmaceutical carrier suitable for enteral or parenteral administration. The formulations may be in solid form, as for example tablets and capsules, or in liquid form as for example syrups, elixirs, emulsions, and injectables. In the formulation of pharmaceutical dosage forms there generally is utilized excipients as for example, water, gelatin, lactose, starches, magnesium stearate, talc, vegetable oils, benzyl alcohols, gums, polyalkylene glycols, and petroleum jelly. Preferred formulations are more fully illustrated in Example 6.

Although the required dosage will be determined by such factors as the patient's age, sex, weight and the severity of the allergic reaction to be treated, the preferred human dosage range is likely to be 4 to 50 mg of the effective compound 1 to 3 times per day. The preferred dosage ranges for other animals can readily be determined by using standard testing methods.

The following Examples are illustrative of the aforementioned pharmaceutical compositions:

Example 6

A syrup comprising a compound of the present invention (Active Compound) is prepared from the following ingredients:

	per ml
Active Compound	0.100 mg
Sucrose	600 mg
Sorbitol	140 mg
Propylene Glycol	20.0 mg
Methylparaben	1.00 mg
Propylparaben	0.200 mg
F.D. & C. Yellow No. 6	0.225 mg
Alcohol USP	0.0021 ml
Limitation Black Currant Flavor	0.001 ml
Purified Water USP	q.s.
	1.0 ml

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The syrup is prepared by combining the above ingredients according to standard techniques.

Cl % Example 7

A tablet comprising a compound of the present invention (Active Compound) is prepared by a spray-dry process from the following ingredients:

Component I	mg/tablet
Active Compound	1.00
Lactose, Hydrous USP (Impalpable Powder)	212
Polyvinylpyrrolidine Povidone NF	10.0
Corn Starch (Food Grade)	15.0
Purified Water USP (Evaporates)	0.102 ml
Additional Components	
Corn Starch (Food Grade)	11.5
Magnesium Stearate USP	0.500

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The materials of Component I are combined and spray dried by standard techniques. The resulting spray dried material is combined with the additional components listed above and processed to form tablets.